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(54) Title: METHOD FOR INVESTIGATING NEUROLOGICAL FUNCTION

(57) Abstract: A method for investigating neurological function, especially parameters in neurological function that are associated with disease. The method uses electroencephalographic (EEG) potentials generated by the workings of the brain combined with cognitive activation procedures or tasks to allow the investigation of neurological functions of the brain. The collection of brain electrical signals in conjunction with the subjects carrying out one or several cognitive tasks allows the responses to be compared either to the results of other subjects or to results obtained from the same subjects under different conditions.

1 **METHOD FOR INVESTIGATING NEUROLOGICAL FUNCTION**

2

3 The present application relates to a method for
4 investigating neurological function, especially
5 parameters of neurological function that are associated
6 with disease. Similar implementations of the method may
7 be created for different neurological diseases which are
8 amenable to useful clinical assessment by this method.

9 It relates in particular to a method of investigating
10 neurological function which incorporates (a) High channel
11 count EEG; (b) cognitive activation procedures ("tasks");
12 (c) a pre-constructed normative database based on
13 specific cognitive activation procedures carried out with
14 relevant healthy and/or clinical populations; and (d)
15 software-based computational procedures which use an
16 individual's test data together with the relevant
17 database to provide information such as classification
18 and severity measures as an aid to clinical diagnosis.

19

20 The key innovative aspect of this invention involves the
21 combined use of cognitive tasks with EEG for the purpose
22 of diagnosing central nervous system disorders in

1 individuals. EEG has a long history of clinical use, but
2 the method proposed in this application is fundamentally
3 different to existing clinical uses (cf. La Rue, A.
4 (1992), Aging and Neuropsychological Assessment, Plenum
5 Press: New York, page 46). For individual clinical
6 diagnosis of neurological disorders, EEG alone is used
7 but not combined with cognitive tasks. A particular form
8 of EEG called "evoked potentials" is used to assess
9 sensory function (Brainstem Auditory Evoked Potentials,
10 Visual Evoked Potentials), but not cognitive function.
11 Cognitive tasks are used in some diagnostic applications,
12 but not combined with EEG. Current clinical practice does
13 not include the application of cognitive tasks combined
14 with EEG for diagnosis of neurological disorders, in fact
15 the abovementioned references show that current knowledge
16 teaches away from the ideas disclosed herein.

17

18 Common neurological health problems include the Primary
19 Degenerative Dementias (e.g., Alzheimer's disease, Lewy
20 Body Dementia, Vascular Dementia), Affective Disorders
21 (e.g., Depressive Disorder), Parkinson's disease, stroke,
22 schizophrenia, multiple sclerosis, addictive disorders,
23 dyslexia, autism, and attention deficit disorders.

24

25 Each of these present problems in diagnosis, monitoring,
26 and optimising therapy. Tools to assist in these efforts
27 are often non-existent, unavailable, or of very limited
28 value.

29

30 As an illustration, the principal symptoms of both
31 Alzheimer's disease and depression are degradation of
32 memory and concentration. A definitive diagnosis often
33 proves very difficult to achieve based solely on clinical
34 presentation, and there are as yet no known biological or

3

1 radiological investigations that can reliably determine
2 the nature of the primary disorder. The existence of
3 other forms of dementia (e.g., vascular dementia) with
4 similar presentations further complicates the diagnostic
5 picture.

6

7 Better diagnostic tools are becoming increasingly
8 important as the range of treatment options for
9 neurological disorders increases. For example, effective
10 treatments for affective disorders (e.g., antidepressant
11 medication) have been available for many years, but very
12 recently several new options for treating Alzheimer's
13 Disease have become available. Though not yet available
14 for clinical use, the advent of general neuroprotective
15 agents offer the possibility that previously untreatable
16 disorders can be effectively treated, provided they can
17 be clearly diagnosed at early enough stages. One goal of
18 clinical practice has been to ensure that patients always
19 receive the available treatment. To meet this goal,
20 methods are required which will increase diagnostic
21 accuracy and help to reduce the risk of inappropriate
22 therapies.

23

24 Alzheimer's Disease is a progressive degenerative disease
25 of the brain and is the most common form of dementia,
26 affecting more than 10% of people over the age of 65. As
27 well as the human cost of Alzheimer's Disease, the
28 financial implications associated with this pathology
29 exceed \$100 million annually in the US alone at the
30 present time. Furthermore, the incidence of Alzheimer's
31 Disease is predicted to increase in the future because
32 the population is ageing.

33

1 A major problem in the treatment of Alzheimer's Disease
2 at the present time is that there exists no conclusive
3 diagnostic test which can be used to confirm that the
4 patient has Alzheimer's Disease. Currently, the only
5 definitive diagnosis that can be made is by post mortem
6 examination. Due to the lack of a conclusive test it. is
7 difficult to know which people really have the disease.
8 It is therefore difficult to know who should be treated.

9

10 If it were possible to detect Alzheimer's Disease earlier
11 in its progression then treatment could be improved.
12 Furthermore, it would be easier to exclude Alzheimer's
13 Disease as a possible cause of symptoms in unaffected
14 patients.

15

16 The value of an early stage diagnostic tool for
17 Alzheimer's Disease is shown in a report issued by The
18 Ronald and Nancy Reagan Institute, which has as its top
19 priority the aim of accelerating the discovery of
20 treatments that can intervene in the progression of
21 Alzheimer's Disease before symptoms appear. The Reagan
22 Institute predicts that a five year delay at the onset of
23 symptoms could cut the number of people inflicted by
24 half, saving \$50 billion annually in the United States.

25

26 Therefore, there is an exceptional demand for tools for
27 use in diagnosis of Alzheimer's Disease and other
28 neurological and psychological disorders. Although this
29 has been an aim of medical research for decades, there
30 remains at the present time an important unmet need for
31 tests suitable for use in diagnosis.

32

33 As mentioned above, the only current method of providing
34 a definitive diagnosis of Aizheimer's Disease can be

1 carried out only after the death of a patient. Current
2 clinical practice in Alzheimer's Disease diagnosis relies
3 mainly on a range of paper-and-pencil tests, and
4 occasional anatomical imaging, administered by a variety
5 of health professionals including neuropsychologists,
6 psychiatrists, radiologists, and others. Rather than
7 identifying characteristic markers of Alzheimer's
8 Disease, current clinical tests aim to exclude other
9 possible diagnoses.

10

11 The state of the art in detection of Alzheimer's Disease,
12 particularly through paper-and-pencil type tests is
13 summarised in the paper "The nature and staging of
14 attention dysfunction in early (minimal and mild)
15 Alzheimer's Disease: relationship to episodic and
16 semantic memory impairment". (Richard J Perry et al.,
17 Neuropsychologia 38 (2000) 252-271). This paper, written
18 by an authority in the field, discusses a variety of
19 neuropsychological tests concluding that one of the most
20 successful is the so called Stroop test in which subjects
21 read out words, red, green, blue, tan that are printed in
22 ink of an incongruous colour e.g. the word red is printed
23 in blue. Patients then read another list of colour
24 names, this time they name the colour of ink in which the
25 word is printed instead of the actual word that is
26 written. However, the best pencil-and-paper tests known
27 miss many early-stage Alzheimer's Disease symptoms, and
28 frequently cannot reliably distinguish Alzheimer's
29 Disease from other diseases.

30

31 Many clinicians claim diagnostic success using interviews
32 and medical histories of a patient. These are known to
33 be up to 85% correct for patients with advanced disease
34 who do not have other diseases and are not taking

1 medications; unfortunately the elderly often have other
2 diseases which confuse diagnosis. The practical level of
3 confidence is usually in the order of 75%.

4

5 The disadvantages of this subjective approach are,
6 firstly, that the results cannot be fully trusted. A 75%
7 confidence level leads to the risk of missing an
8 unacceptable number of patients and of unnecessarily
9 worrying and treating some patients who do not in fact
10 have the disease. Secondly, subjective approaches can
11 only be carried out successfully once the disease is
12 already highly advanced. A third disadvantage of the
13 subjective techniques is that they can only be carried
14 out by a skilled clinician whose time is expensive.
15 Several interviews of, say, one hour each are required.

16

17 A supplementary approach to diagnosis is brain scanning.
18 For example, CAT and SPECT scans have been used to
19 monitor changes in brain blood flow which are thought to
20 be implicated in the development of Alzheimer's Disease.
21 These scans have proved able to add confidence of the
22 diagnosis of Alzheimer's Disease, but the scanning
23 techniques are not without their drawbacks. The cost of
24 the scanning equipment is high, and repeat testing
25 increases the danger of exposure to radioactive isotopes.
26 Furthermore, the scanning techniques have mainly been
27 tried out in difficult to diagnose patients who already
28 have advanced symptoms and have not been proved
29 efficacious for early stage patients

30

31 Another method that has been used in diagnosis of
32 Alzheimer's Disease is genetic screening. However, there
33 is no single gene for Alzheimer's Disease and as
34 Alzheimer's Disease is common amongst the ageing

1 population, having an elderly relative with Alzheimer's
2 Disease is not fully predictive of a familial link.

3

4 Variations in the genes ApoE 2, ApoE 3 and ApoE 4 are
5 thought to influence Alzheimer's Disease risk. However,
6 genetic testing can only show who is at risk, not whether
7 the disease has started in a particular individual.
8 Widespread screening is unlikely to positively influence
9 the outcome of Alzheimer's Disease progression. Genetic
10 testing is certainly not an early onset diagnostic
11 technique.

12

13 The aim of the present invention is to provide a method
14 of assessing aspects of brain function known to be linked
15 in some circumstances to neurological and psychological
16 disorders and thereby to provide information which can be
17 used by a clinician in making a diagnosis. Ideally, the
18 invention aims to provide an early onset test which can
19 be applied accurately whilst the disease is still in its
20 early stages allowing treatment to be begun. The
21 invention aims also to provide a test which is economic
22 and which can be carried out quickly and easily by
23 technicians rather than requiring the time of highly
24 trained clinicians. The test can be applied repeatedly
25 to an individual, and so can serve not only as a
26 diagnostic tool but also as an aid to ongoing management
27 of therapy.

28

29 Although the use of this technique for detecting
30 Alzheimer's Disease is the primary focus of this example
31 description, the technique will also be applied to other
32 aspects of brain function, particularly diseases such as
33 Parkinson's disease, depression, stroke, schizophrenia,
34 multiple sclerosis, addictive disorders, dyslexia,

1 autism, and attention deficit disorders. Detection of
2 these and other disorders which have disruption or change
3 to higher cognitive functions among their primary
4 symptoms is an additional aim of the invention herein
5 disclosed.

6

7 According to a first aspect of the present invention
8 there is provided a method of characterising an aspect of
9 the neurological function of a subject comprising the
10 steps of:

11

12 (a) providing stimuli to a subject, said stimuli
13 being chosen to cause the subject to carry out a
14 particular neurological act;

15

16 (b) monitoring the electroencephalographic (EEG)
17 response of the brain whilst said neurological act
18 is carried out; and

19

20 (c) comparing said response of the brain with a
21 database of normative responses in trial subjects,
22 said database also containing information about an
23 aspect of neurological health of those trial
24 subjects.

25

26 (d) the use of statistical methods to carry out said
27 comparison which are appropriate to the task of
28 characterising an individual's test data as an aid
29 to clinical diagnosis and management of therapy.

30

31 According to a second aspect of the present invention
32 there is provided a method of characterising an aspect of
33 the neurological function of a subject comprising the
34 steps of:

1

2 (a) providing stimuli to a subject, said stimuli
3 being chosen to cause the subject to carry out a
4 particular neurological act;

5

6 (b) monitoring the electroencephalographic (EEG)
7 response of the brain whilst said neurological act
8 is carried out; and

9

10 (c) comparing said response of the brain in a
11 subject or group of subjects, where the subjects
12 are, or subject is, at different stages of treatment
13 with a therapeutic, which includes pre- and post-
14 treatment; and

15

16 (d) using statistical methods to carry out said
17 comparison, which are appropriate to the task of
18 characterising test data as an aid to commercial
19 research and testing of therapeutics.

20

21

22 Preferably, the aspect of neurological function of a
23 subject which is characterised is a parameter associated
24 with the presence or absence of a neurological disease.

25

26 More preferably, the neurological disease is one which is
27 known or suspected to cause changes to higher cognitive
28 function such as memory, attention and language.

29

30 Preferably, the EEG potentials are measured by a sensor
31 array applied to the subject's head.

32

10

1 Most preferably, at least a 128 channel sensor array is
2 used to measure EEG potentials on the surface of a
3 subject's head.

4

5 Preferably, the stimuli are auditory, visual, and/or
6 tactile.

7

8 Typically, the subject will be required to carry out
9 actions in response to stimuli.

10

11 The aspect of neurological function may be memory and the
12 stimuli may preferably be repetitive presentation of
13 information, with the subjects being required to make a
14 response indicating whether they recognise information
15 presented to have been repeated.

16

17 The aspect of neurological function may be response
18 inhibition and the stimuli may preferably be the
19 presentation of number words in one of a plurality of
20 colours superimposed over bars, with the subject being
21 required to respond to the word or the bar depending on
22 the colour in which the number word is presented.

23

24 The aspect of neurological function may be the ability to
25 dynamically change a response selection rule in a choice
26 task and the stimuli may preferably be two different
27 visual images, with the subject being required to make
28 one response to one visual image and a second response to
29 a second visual image, wherein the subject is
30 periodically required to swap the responses made to the
31 visual stimuli.

32

33 The aspect of neurological function may be
34 interhemispheric transfer and the stimuli may preferably

11

1 be visual or auditory stimuli presented to either the
2 left or right visual field or ear of the subject wherein
3 the subject is required to make a response to indicate
4 perception of the stimuli, wherein the specific peak
5 latency of the left and right hemispheres of the brain
6 are separately measured and the difference between these
7 times is calculated.

8

9 The aspect of neurological function may be language
10 comprehension and/or production ability and the stimuli
11 may preferably be visual or auditory language or other
12 symbolic representations, with the subject being required
13 to make responses either verbally or manually which
14 indicate operation of a particular language function,
15 especially those subject to selective impairment by
16 neurological disease or damage.

17

18 The response of the brain to more than one set of stimuli
19 may be measured.

20

21 The responses of the brain to more than one different set
22 of stimuli may, in an otherwise known method, be taken
23 into account simultaneously and compared with the
24 database of responses in trial subjects.

25

26 The invention will now be described by way of example
27 only with reference to the following Figure in which:

28

29 Figure 1 shows in perspective view the key apparatus
30 used in the present invention.

31

32 The subject of this application is a new method for
33 measuring aspects of neurological function. In
34 particular, the following example describes the invention

12

1 being applied to the detection of a disease which
2 primarily affects elderly people.

3

4 The test is composed of one or several cognitive tasks
5 which are employed in combination with the collection of
6 brain electrical signals. Essentially, the patient's
7 brain is driven by the tests to carry out specific
8 neurological functions. Multiple measurements of brain
9 electrical signals and behavioural responses are then
10 collected, analysed by statistical methods, compared
11 against a database of results from diseased and normal
12 patients and used to provide an index value which can be
13 used by a clinician. Furthermore, results from multiple
14 tests and multiple measures from individual tests may be
15 analysed together, providing further indices of greater
16 accuracy and disease specificity.

17

18 Important innovative elements of this test are the
19 specific designs of the cognitive tasks and the use of
20 time-locked EEG (evoked potentials) to measure the
21 brain's response during task performance.

22

23 Referring to Figure 1, a patient 1 sits in front of a
24 test controlling computer 2 which has a VDU 3, input keys
25 4 and audio speakers 5. A dense-array EEG system 6 is
26 affixed to their head to measure EEG potentials across
27 the head surface as time series. In the present example,
28 a commercial (128-channel) digital dense-array EEG system
29 is used.

30

31 The tasks in the diagnostic tool are designed to tap into
32 features of perceptual and higher cognitive function that
33 are known to deteriorate relatively early in the disease
34 process. These include memory, attention, language, and

1 certain vision and audition processes. More
2 specifically, the VDU 3 and headphones 5 provide
3 instructions to the patient to perform a battery of tasks
4 designed to tap into perceptual and higher cognitive
5 functions including memory, attention and language.
6 Measurements of brain electrical function are collected
7 during task performance by means of the EEG system 6.

8

9 EEG responses are measured by a data processing computer
10 7, connected to the sensor array 6 by a plurality of
11 wires 8. The data processing computer 7 evaluates the
12 potentially pathological patterns of brain activity in a
13 clinical subject by comparing them against a database of
14 appropriately normed data from healthy and known
15 pathological samples. By objectively comparing resultant
16 data with appropriate populations norms, indicators
17 pointing to an evaluation of the presence and graded
18 severity of a pathological brain state are calculated.

19

20 Database

21

22 Elderly healthy subjects volunteer to participate in test
23 sessions. Possible patients are then compared against
24 the baseline provided by the elderly (i.e., age-matched)
25 healthy subjects. This provides a measure of the decline
26 in cognitive brain performance due to the neurological
27 disorder, over and above the effects of normal ageing.
28 In practice, clinicians will use the test battery to
29 obtain a data set from a candidate patient and then use
30 this information in forming their diagnosis. The results
31 will then be compared against an appropriate subset of
32 the normative database. Objective measures of deviation
33 can be quantified and charted, providing the clinician a

1 concise summary of key markers characteristic of the
2 neurological disorder versus normal performance.

3

4 Apparatus

5

6 The commercial EEG systems 6 are supplied by Electrical
7 Geodesics Inc (Eugene, OR, USA). The system consists of
8 an amplifier, several sizes of electrode nets, control
9 computers and control software. A custom user interface
10 shell to enslave the EGI software is provided in the
11 invention herein disclosed.

12

13 Data outputs from the battery of tests may be used to
14 prepare parameters based on the results of individual
15 tests. However, it is known that individual changes in
16 brain function may be caused by more than one pathology.
17 This is why more than one test may be required in
18 diagnosis of some neurological pathologies.

19

20 In a further embodiment of the present invention it is
21 recognised that results from more than one of the tests
22 may be fed into known mathematical processing techniques
23 to provide measurements correlated with diagnoses of
24 diseases which are more specific to individual
25 pathologies than results of individual tests.

26

27 In a yet further embodiment of the present invention, the
28 imaging capability of the geodesic EEG sensor array is
29 utilised further. Aspects of neurological function are
30 often localised to individual parts of the brain. This
31 can be extended by providing tests which drive individual
32 areas of the brain to carry out tasks and by then
33 measuring parameters of the EEG response of those
34 individual areas of the brain.

1

2 The tests described herein will be useful for clinicians
3 who are responsible for diagnosis and management of
4 neurological disorders which affect higher cognitive
5 function and for pharmaceutical companies requiring
6 sensitive tests of drug action aimed at neurological
7 disorders which affect higher cognitive function. In the
8 latter case, group comparisons may be preferred to
9 individual diagnoses.

10

11 Throughout this application, unless the context requires
12 otherwise, the word "comprise" or variations such as
13 "comprises" or "comprising" will be understood to imply
14 the inclusion of a stated integer or group of integers
15 but not the exclusion of any other integer or group of
16 integers. Also the term "neurological" in this document
17 is meant to encompass both neurological and psychiatric
18 functions.

19

20 Further improvements and modifications clear to one
21 skilled in the art may be made within the scope of the
22 invention herein described.

1 CLAIMS

2

3 1. A method of characterising an aspect of the
4 neurological function of the subject comprising the
5 steps of:

6

7 (a) providing stimuli to a subject, said stimuli
8 being chosen to cause the subject to carry out
9 a particular neurological act; and

10

11 (b) monitoring the electroencephalographic response
12 (EEG) of the brain whilst said neurological act
13 is carried out.

14

15 2. A method of characterising an aspect of the
16 neurological function of a subject, as in Claim 1,
17 comprising the additional steps of:

18

19 (c) comparing said response of the brain with a
20 database of normative responses in trial
21 subjects, said database also containing
22 information about an aspect of neurological
23 health of these trial subjects; and

24

25 (d) using statistical methods, to carry out said
26 comparison, which are appropriate to the task
27 of characterising an individuals test data as
28 an aid to clinical diagnosis and management of
29 therapy.

30

31 3. A method of characterising an aspect of the
32 neurological function of the subject comprising the
33 additional steps of:

34

- 1 (c) comparing said response of the brain in a subject or
2 group of subjects, where the subject is, or the
3 subjects are, at different stages of treatment with
4 a therapeutic, which includes pre and post
5 treatment; and
6
- 7 (d) using statistical methods, to carry out said
8 comparison, which are appropriate to the task of
9 characterising test data as applied to commercial
10 research and testing of therapeutics.
11
- 12 4. A method of characterising an aspect of the
13 neurological function of a subject, as in any of the
14 previous Claims, wherein the aspect of neurological
15 function of the subject which is characterised is a
16 parameter associated with the presence or absence of
17 a neurological disease.
18
- 19 5. A method of characterising an aspect of the
20 neurological function of a subject, as in Claim 4,
21 wherein the neurological disease is one which is
22 known or suspected to cause changes to higher
23 cognitive functions, such as memory, attention and
24 language.
25
- 26 6. A method of characterising an aspect of the
27 neurological function of a subject, as in any of the
28 previous Claims, wherein the EEG potentials are
29 measured by a sensor array applied to the subject
30 head.
31
- 32 7. A method of characterising an aspect of the
33 neurological function of a subject, as in Claim 6,

18

1 wherein the multi-channel sensor array is at least a
2 128 channel sensor array.

3

4 8. A method of characterising an aspect of the
5 neurological function of a subject, as in any of the
6 previous Claims, wherein the stimuli are auditory,
7 visual and/or tactile.

8

9 9. A method of characterising an aspect of the
10 neurological function of a subject, wherein the
11 subject will be required to carry out actions in
12 response to stimuli.

13

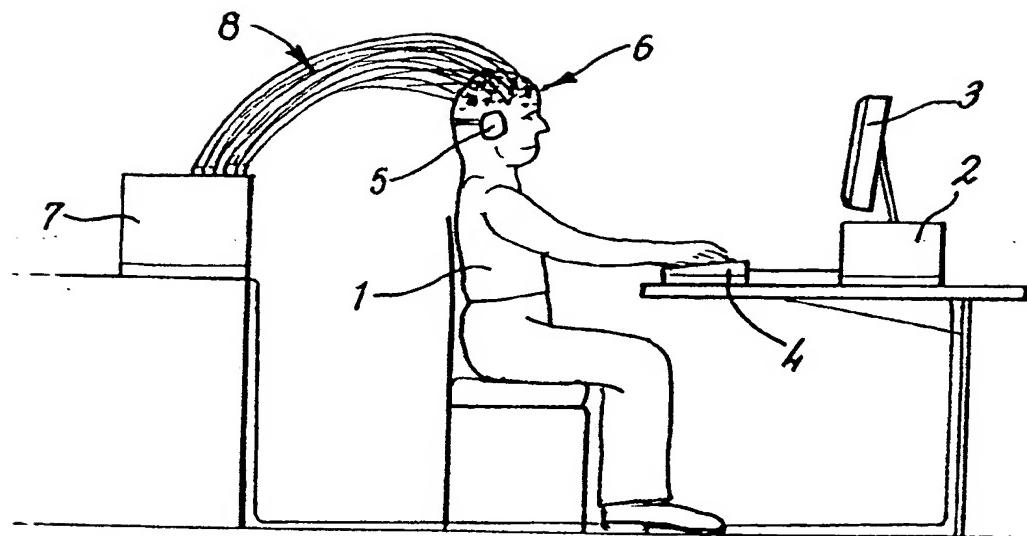


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/00697

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/0484

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 59469 A (SWINBURNE) 25 November 1999 (1999-11-25) page 1, line 27 -page 3, line 7 page 5, line 30 -page 13, line 31 page 18, line 4 -page 20, line 8 figures 1-3A claims 1-17	1
A		2, 3, 6, 8, 9
X	WO 91 09565 A (SWINBURNE LIMITED) 11 July 1991 (1991-07-11) page 20, line 14 -page 21, line 16 page 25, line 3 -page 33, line 23 page 46, line 16 -page 48, line 1 figures 1,2	1
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 984 578 A (KEPPEL) 15 January 1991 (1991-01-15) column 2, line 24 - line 54 column 3, line 3 - line 38 column 4, line 14 -column 7, line 51 figure 3 ---	1
X	US 4 736 751 A (GEVINS ET AL.) 12 April 1988 (1988-04-12) abstract column 3, line 60 -column 5, line 7 column 6, line 30 -column 9, line 6 figure 4 ---	1
X	WO 93 03670 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 4 March 1993 (1993-03-04) page 3, line 36 -page 5, line 37 page 14, line 21 -page 25, line 31 page 38, line 5 -page 43, line 6 figures 9,10 ---	1
A		2,3,6,8, 9

INTERNATIONAL SEARCH REPORT

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